Long-term outcome of infliximab in severe chronic and refractory systemic sarcoidosis: a report of 16 cases

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Abstract

Objective

Infliximab (IFX) appears to be effective in refractory sarcoidosis. However, data are lacking regarding its efficacy in severe sarcoidosis (i.e. with cardiac and/or neurological involvement).

Methods

Retrospective single-centre study including 16 unselected consecutive patients with biopsy proven, severe, and resistant sarcoidosis, who were treated by infliximab (3 or 5 mg /kg at 0, 2 and 6 weeks, then every 8 weeks) between 2005 and 2013.

Results

Following IFX therapy we observed an improvement in 92% of cases, with a marked decrease of the severity score [median score 6 (3–12) vs. 2 (1–8), p<0.0001] and trend toward steroid sparing effect [12.5 (0–40) vs. 8.5 mg/d (0–30), p=0.11] between baseline and the end of follow-up, respectively. Regarding the index organ response, we observed a remission of cardiac and central nervous system involvements in 4 out of 4 and 11 out 12 cases, respectively. Thirty-eight percent of patients experienced a relapse. After a median follow-up of 57 months (2 to 91), we observed 7 (44%) infectious complications, 1 paradoxical cutaneous granuloma and 1 leucoencephalopathy. Infectious complications were mostly observed in male [6/7 (86%), p=0.06], with a longer duration of steroids (108 vs. 39 months, p=0.11) and immunosuppressant use prior IFX (42 vs. 24 months, p=0.08) compared to their negative counterpart, respectively.

Conclusion

IFX was efficient in severe and refractory sarcoidosis. Infectious complications were frequent and occurred mainly in male patients with longer duration of steroids and immunosuppressant use prior to IFX.

Key words

systemic sarcoidosis, infliximab, cardiac, neurologic involvement

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Introduction

Sarcoidosis is a systemic granulomatous disease of unknown aetiology, which may involve many different organs. Usually, the course is benign with a high rate of remission, whether spontaneously or with treatment. Sarcoidosis can be chronic and progressive in 25% of patients with a risk of organ dysfunction. Treatment of sarcoidosis is not standardised even if corticosteroids are the first line therapy. In cases of lack of response or unacceptable side effects, steroids are supplemented with other immunosuppressive therapy such as methotrexate (MTX), cyclophosphamide (CPM), mycophenolate mofetil (MMF), azathioprine (AZA) and recently with tumour necrosis factor-alpha (TNF-α)-inhibitors (1-11). Tumour necrosis factor-alpha (TNF-α) plays a significant role in antigen-stimulated, cell-mediated immune responses and in the pathogenesis of non caseating granulomatous inflammation. TNF-α is released by macrophages and is elevated in alveolar macrophages of bronchoalveolar lavage during sarcoidosis (12). In the past, the efficacy of other anti TNF agents such as pentoxifylline and thalidomide has been observed in sarcoidosis (13, 14). No clinical trial comparing the efficacy of different TNF-α inhibitors in sarcoidosis is currently available. Infliximab has mostly been used and was associated with successful results in sarcoidosis both in cases reports and randomised trials, particularly in cutaneous, ocular or pulmonary sarcoidosis (1-9). However, data regarding efficacy of TNF-α inhibitors in cardiac and central nervous system involvement of sarcoidosis are scarce.

In the present study, we report the long-term outcome of infliximab (IFX) in 16 patients with severe sarcoidosis (*i.e.* mainly with central nervous system and/or cardiac involvements), refractory to steroid and immunosuppressive therapy.

Materiel and methods

Patients

This is a retrospective single-centre study including 16 unselected consecutive patients with chronic, severe, and resistant sarcoidosis, who were treated by infliximab between 2005 and 2013. We included patients only with histologically-proven sarcoidosis (Fig. 1). For neurological and cardiac sarcoidosis, all patients responded to the international criteria (15, 16). At sarcoidosis diagnosis, patients were defined as severe when presenting with ≥3 organ involvements, with functional or vital risk (*i.e.* mainly with central nervous system and/or cardiac involvements). For assessment of the index organ severity (*i.e.* primary target organ supporting IFX prescription), we used the score proposed by Judson *et al.* in a previous study (Tables I-II) (17). This score was used only for the index organs before and after IFX therapy, considering that other organs involved at diagnosis had been cured. Sarcoidosis was considered as chronic when disease was still active 18 months after the diagnosis. Refractory sarcoidosis was defined as patients non responders to steroid therapy (1 mg/kg/d of prednisone) and at least to one (4 patients) or more immunosuppressive agents (12 patients). Before infliximab, we systematically searched for latent tuberculosis (negative interferon γ release assay). Patients with serious and /or chronic infection within 2 months and malignancy history were excluded. Nine patients without biopsy proven sarcoidosis and two cases lost to follow-up were excluded (Fig. 1).

The following data were collected: age, gender, ethnic group, organs involved and the severity score of index organ appreciated on clinical examination and with appropriate paraclinical results (ocular examination, nose endoscopy, laboratory study, cerebrospinal fluid analysis, lung function tests, chest CT scan, cerebral magnetic resonance imaging (MRI), electrocardiography, cardiac MRI, cardiac scintigraphy, joint MRI).

The following data regarding treatments were collected: dosage of steroids before and after TNF-α inhibitors, associated immunosuppressive therapy (IST) before, during and after infliximab, and dosage and duration of IFX. Finally, the efficacy and side effects under IFX and the reason of premature treatment interruption were recorded.

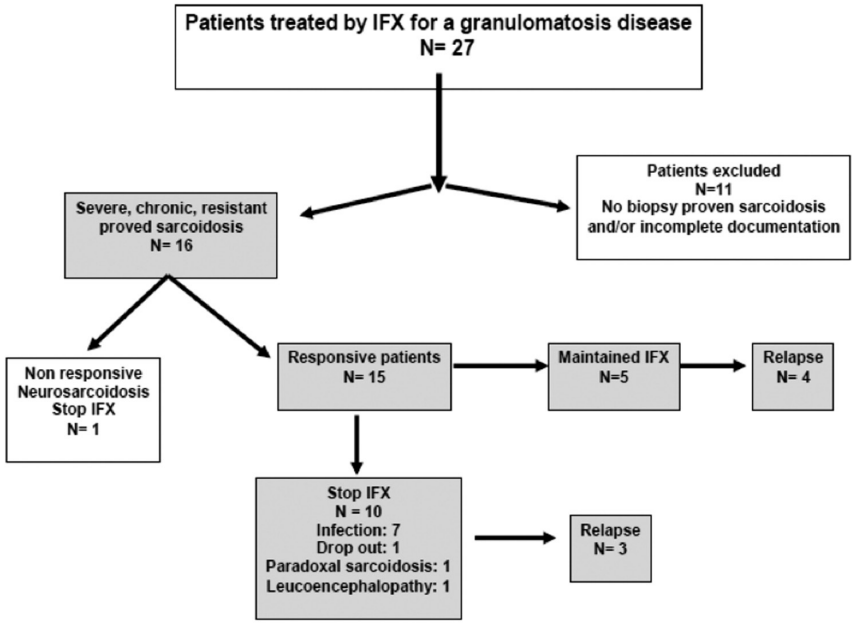

Fig. 1. Flow Chart and outcome of the study population.

Therapeutic modalities

Intravenous infusions of IFX were proposed at 3 or 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. The lowest dosage (3 mg/kg) was proposed to the first patients treated by IFX. In case of suboptimal response, IFX dosage was increased up to 7.5 mg/kg and/or the interval between two perfusions was reduced to 6 or 4 weeks. During this treatment, concomitant medication including corticosteroids and methotrexate was proposed to 10 patients. In 4 cases, prednisone was stopped, in one case because of patient refusal, in 3 cases because of severe osteoporosis. Nevertheless, disease worsening led to resume prednisone in these 3 patients. During IFX therapy, methotrexate was not prescribed in 3 cases, because of historically patient proven therapeutic inefficiency in 2 cases and due to severe hepatic granulomatosis in 1 case. Clinical follow-up was individualised and was tailored to the index organ for which IFX was prescribed. A clinical evaluation was performed before and after each infusion of IFX. All patients underwent serial physical examination, biological tests (ACE but not sIL-2R) and imaging screening with morphologic data to control involved organs. Due to the retrospective aspect of the study, 18F-FDG PET data are available for a very limited number of patients.

Treatment efficacy

Response to treatment has been defined as an objective clinical improvement. As for MRI (cardiac, cerebral or joint), gadolinium-enhancement demonstrating improvement of lesions before and after IFX was assessed. All patients presented a normal ACE dosage as a result of immunosuppressive treatment before IFX therapy. sIL-2R dosage was not performed. We have no comparative data on ^{18}FDG-PET scan. Response could be complete or partial. Complete response was defined by the absence of functional signs and a normalisation of imaging. Partial response was defined by the persistence of physical signs and/or abnormal imaging. Therapeutic failure was defined as the absence of clinical and/or laboratory improvement. The severity score (Table I) was calculated only for organs involved just before IFX thus defining the index organ which was calculated before infliximab and at the end of follow-up. The steroid sparing effect was evaluated by comparing prednisone dosage at baseline and after IFX last injection.

Statistical analysis

Quantitative variables are presented as median (interquartile range, IQR, or range) and were compared using Wilcoxon's rank sum test. Qualitative variables are presented as count (percent) and were compared using Fisher's exact test. Comparisons between baseline and end of follow-up values were tested using Wilcoxon's rank sum paired test. All tests were two-sided at a 0.05 significance level. Analyses were performed with R statistical software, version 2.15.2 (http://www.R-project.org/).

Table I. Severity assessment of each organ before infliximab use (17).

Score	Description
0	Not affected
1	Slight
2	Mild
3	Moderate
4	Moderate to severe
5	Severe
6	Very severe

Results

Baseline characteristics

Sixteen patients with chronic resistant and severe sarcoidosis were included (Fig. 1). The baseline characteristics, index organ, and the severity score assessment are summarised in Table II. The sex ratio (female/male) was 0.78, with a median age of 36 years (range 14 to 73, IQR 26 to 43). In all cases, the disease was chronic with a median duration of sarcoidosis of 91 months (range 19 to 415, IQR 36 to 125). The disease was severe as 75% of patients had three or more affected organs and most patients had neurological (12 cases) and/or cardiac (5 cases) involvements. At baseline, the median activity score was of 6 (range 3 to 12, IQR: 5 to 8). Treatment histories and the immunosuppressive therapy before infliximab are listed respectively in Table III and Table IV. Previous IST used before IFX included cyclophosphamide (CYP) (cyclophosphamide: 1g per month) in 6 cases, methotrexate (MTX) (0.3 mg per week) in 5, mycophenolate mofetil (MMF) (2–3g/d) in 1case, etanercept (ETC) (25 mg per week) in 1 cases and MMF plus MTX in 1 patient. The median duration of steroids and IST use prior IFX was of 49 months (range 14 to 144, IQR: 33 to 92 months) and 28 months (range 9 to 110, 24 to 44 months), respectively. The initial dosage of IFX was 3 mg/kg

Table II. Baseline characteristics of the 16 patients with sarcoidosis*.

Variable	n. (%)
Age to diagnosis (years)	36 (26 to 43)
Sex ratio: female/male	7/9 (78)
Race	
-White	6 (38)
- Black	5 (31)
- Maghreb	4 (25)
- Asian	1 (6)
Time since sarcoidosis histologically proven (months)	91 (36 to 125)
Number of patients with ≥3 organs involved	12 (75)
Severity score of index organ before IFX	6 (5 to 8)
Duration of steroids before IFX (months)	49 (33 to 92)
Duration of IST before IFX (months)	28 (24 to 44)
IST from diagnosis to IFX	
- cyclophosphamide	13 (81)
- methotrexate	11 (69)
- mycophenolate mofetil	5 (31)
- azathioprine	1 (6)
- etanercept	1 (6)

*Except where indicated data are expressed as number, (%) or median (IQR).
IST: immunosuppressant; IFX: infliximab.

Table III. organs involved at diagnosis and before IFX.

Organs involved	At diagnosis	Before IFX
Central nervous system	12	12
Cardiac	5	4
Pulmonary	14	3
Cutaneous	2	1
Ocular	6	1
Intra-abdominal lymph nodes	2	1
Liver	1	1
Joint	2	1

Table IV. Outcome of the 16 patients with sarcoidosis under infliximab (IFX).

Variable	Before IFX	After IFX	*p*-value
Dosage of steroids	15 (0-30)	8.5 (0-30)	0.11
Severity score	6 (3-12)	2 (1-8)	<0.001
Number of index organs	24	1	<0.0001
Cyclophosphamide	13 (81)	1 (6)	<0.0001
Methotrexate	11 (69)	10 (62)	0.60
Mycophenolate mofetil	5 (31)	1 (6)	0.030
Etanercept	1 (6)	0	
Azathioprine	1 (6)	0	

in 5 patients and 5 mg/kg for the remaining 11 patients. Except in one case (hepatic contraindication), infliximab was always associated to steroids and/or methotrexate.

Efficacy

After a median follow-up of 57 months (range: 2–91) no death was observed. The mean number of IFX infusions was 15 (range: 2–42). One early (after the second infusion) severe infection led to immediate stop of IFX treatment. All others received at least 6 infusions. Out of the 5 patients who received 3 mg/kg as initial dosage of IFX, 3 were responders and 2 with incomplete response received 5 mg/kg or more. At the end of follow-up, a favourable response (partial remission in 9 cases and complete remission in 6 cases) was noted in 94% of cases (15/16). Improvement was observed in all cases but one, with a significant improvement of the severity score (median score at baseline 6 (3–12) *vs*. 2 (1–8) at the end of follow-up, $p<0.001$) and trend toward steroid sparing effect (median dose at baseline 15 (0-30) *vs*. 8.5 mg/d (0-30) at the end of follow-up, $p=0.11$) were noted (Fig. 2, Table IV). The sparing effect was not significant due to the small number of patients. We observed a constant remission of cutaneous, nose, ocular, cardiac, lymph nodes and pulmonary sarcoidosis and a non-response in one out of 12 patients with a central nervous system involvement.

In only 5 patients, IFX was still maintained (IFX group). For those, the median severity score dramatically fell from 5 to 2 at the end point. In this group, a relapse of the index organ was noted in 4 cases (80%) with a less important score probably due to their regular monitoring before dramatic functional signs. They were successfully treated by increased dose of IFX or reduction of infusion intervals. At the end point, the sequences of IFX (5 mg/kg) were spaced of 4 weeks (n=1), 5 weeks (n=1), 6 weeks (n=2) and 8 weeks (n=1) to maintain a sustained remission. Methotrexate and steroids were associated in these 5 cases. Relapse was also observed in 3 of 11 patients who stopped IFX. In these patients, two were successfully treated by classic IST, one worsened. Whatever therapy used the comparative analysis between patients who relapsed and their negative counterpart did not show any difference according to age, sex, race, index organs, duration of the disease, duration of steroids and IST, dose of steroids, score, and choice of IST.

Adverse events

Infliximab was stopped in 11 cases (Fig. 1). The median number of infusions of infliximab was 6 (range: 2 to 24). The reasons for IFX interruption included acute infection in 7 cases [pulmonary infection (n=2); recurrent prostatitis (n=1); aspergillosis infection (n=1); atypic mycobacterium disease (n=1); bacterial sepsis (n=1); multiviral reactivation (n=1), paradoxical granulomatous (n=1), leucoencephalopathy (n=1) and personal choice (n=2)]. Leucoencephalopathy dramatically regressed when infliximab was stopped. For all hospitalised patients, all infections were cured by appropriate anti infectious agents. All sarcoidosis but one

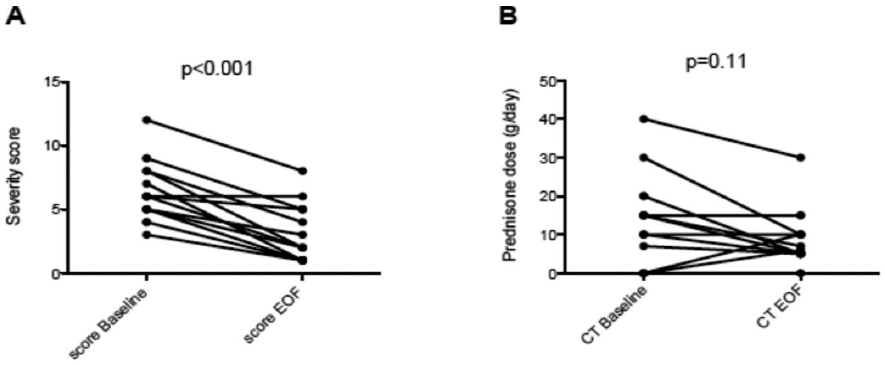

Fig. 2. Course of the severity score (**A**) and of the daily prednisone dosage (**B**) under infliximab in patients with sarcoidosis.

Table V. Comparison according to the occurrence of an infectious complication under IFX in patients with sarcoidosis*.

	Non-infected patient n=9	Infected patients n=7	*p*-value
Age to diagnosis (years)	37 (25 to 42)	31 (28 to 43)	0.84
Sex ratio F/M	1	0.17	0.060
Score before IFX	6 (5 to 6)	7 (4 to 8)	0.1
Time since diagnosis (months)	41 (33 to 95)	117 (91 to 140)	0.25
CPM	7 (83%)	6 (86 %)	1
MTX	6 (67%)	5 (71 %)	1
MMF	3 (33%)	2 (29%)	1
ETC	0	1 (14%)	0.44
AZT	1 (11%)	0	1
Dose of CS before IFX (g/d)	15 (0 to 20)	12 (10 to 15)	0.67
Duration of CS before IFX (months)	39 (33 to 50)	108 (50 to 204)	0.11
Duration of IST before IFX (months)	24 (24 to 29)	42 (32 to 79)	0.080

*Except where indicated data are expressed as median (IQR).
IFX: infliximab; CPM: cyclophosphamide; MTX: methotrexate; MMF: mycophenolate mofetil; ETC: etanercept; AZT: azathioprine; CS: corticosteroids.

in the infectious group were successfully treated again with classical IST (MTX: 5 cases, MMF: 1 case, CPM: 1 case) according to a median follow-up of 52 months (range, 8–85 months) after IFX withdrawal. No difference was seen relative to age, geographic origin, index organ, dose of steroids, severity score, and choice of IST between infected and non-infected patients. Infectious complications were mostly observed in male (86%; p=0.060), with a longer duration of steroids (median, 108 *vs*. 39 months, p=0.11) and IST use prior IFX (42 *vs*. 24 months, p=0.08) compared to their negative counterpart, respectively (Table V). For all patients but one at relapse, we did not find any auto antibodies against IFX.

Discussion

Corticosteroids are the gold standard treatment of sarcoidosis. In approximately 25% of cases, immunosuppressive drugs are associated to steroids. TNF-α inhibitors are effective in sarcoidosis, mainly in cutaneous, ocular or pulmonary lesions (1-9). However, data regarding efficacy of TNF-α inhibitors in cardiac and central nervous system involvement of sarcoidosis are scarce. Our current experience is derived from the largest cohort defined as follows: severe sarcoidosis (≥3 organs involved including cardiac and/or central nervous system), chronic (course before IFX >18 months) and multiresistant to high dose of immunosuppressive therapy. All patients were refractory to the combination of steroids with one (n=3) or 2 IST (n=13) prior IFX therapy. No patient presented any infectious complication before IFX introduction. The most striking conclusions drawn by our study are 1) IFX seems highly efficient in severe and refractory sarcoidosis; 2) IFX treatment discontinuation is frequent and is mainly related to infections; 3) Infectious complications occurred mainly in patients with a longer duration of steroids and IST use prior to IFX and 4) relapses are frequent imposing an increased dose of IFX or a reduction of infusion interval.

Our patients presented with severe and refractory sarcoidosis as 75% had neurological and/or cardiac lesions. We observed an improvement in 94% of cases. Complete remission of cardiac and neurological involvement was achieved in 100% and 92% of cases, respectively. In addition, IFX allowed a significant decrease of the sarcoidosis severity score and a reduction of steroids doses. Most cases series in the literature have demonstrated the efficacy of IFX in resistant sarcoidosis with various localisations (1-9, 16, 17, 20-25). Efficacy of IFX was also observed in cases of interferon alpha associated sarcoidosis (26) and in a resistant hypercalcemia (27). Studies reporting efficacy of IFX in multi organ sarcoidosis are rarer (2, 20). Clinical improvement under IFX was observed in the majority of studies (1-9, 20-25) and was correlated with 18F FDG PET modifications in one study (28). Histological remission was also noted after TNF-α inhibitor's and repeated biopsies showed a resolution of sarcoid granuloma starting with disappearance of macrophages (29). The randomised, double blind, placebo controlled study report by Baughman *et al*. (30) involving 138 patients with chronic pulmonary sarcoidosis showed a rapid significant efficacy of infliximab, especially in patients treated with high dose of steroid or immunosuppressive agents and/or those with multiorgan extrapulmonary involvement. Judson *et al*. (20) demonstrated the beneficial interest of IFX *versus* placebo in extra pulmonary sarcoidosis. In these two studies, patients received before IFX a different immunosuppressive treatment (lower doses, treatment duration, less combination) so no comparative analysis with our data could be performed. Maneiro *et al*. (17) reviewed 69 articles (clinical trials, cases series and case reports) of sarcoidosis treated by TNF-α inhibitors. Overall,

232 patients were treated by infliximab and 26 by etanercept. This review illustrates the diversity of the studies with heterogeneous populations, designs and outcomes across studies. If we consider extra pulmonary localisation, improvement was noted in 80% of cases for cutaneous form, 94.7% for neurosarcoidosis, 85.7% for ocular, 87.5% for cardiac, 66.7% for bones and only 50% in hepatic sarcoidosis. Recently, Judson (7) mention that IFX efficacy is not correlated to an added steroid treatment above 15-20 mg/d *versus* low dosage. Our retrospective study could answer that point. Some characteristics may predict response to IFX like the $CD4^+$ lymphopenic sarcoidosis phenotype (31), or the C-reactive protein level (32). In our series, 11 patients stopped IFX (regardless the reason to stop), and the course was favourable in 10 cases out of 11 while a classic formerly ineffective IST treatment was resumed (methotrexate or cyclophosphamide). After a median follow-up of 52 months after infliximab withdrawal, we observed 3 relapses.

We did not observe anaphylactic or delayed hypersensitivity reaction in our series (1, 17, 20). Out of the 5 patients with available data, we did not observe the production of TNF-α inhibitors antibodies except in one case. Nine out of 16 (56%) patients experienced at least one side effect with IFX, which was severe in 5 cases. A patient with neurosarcoidosis presented leucoencephalopathy, which has resolved 6 months after IFX withdrawal and did not relapse when cyclophosphamide was resumed. One patient presented biopsy proven skin sarcoidosis flares up after 15 IFX cures that regressed after IFX withdrawal and resuming classic treatment (steroids and MMF). In the literature, the adverse events are rare but well known with biotherapy (17, 20, 30, 33). Paradoxical granulomatous reactions (mainly cutaneous and pulmonary and sometimes neurological lesions) related to TNF-α inhibitors have been largely reported (34-36).

In our series, the most frequent adverse event was acute infection in 7 cases, which always lead to treatment withdrawal. Pretreatment profile of infected patients *versus* non-infected ones was quite revealing. Two critical factors were associated with these infectious events; the duration of steroid therapy and the IST duration prior to IFX, both superior to 18 months. In contrast, the number of IST agents and the type of IST used prior to IFX were not different in sarcoidosis patients with and without infectious complication. IFX dosage did not impact the rate of side effects. Taken together, these results suggest that TNF-α inhibitors should be prescribed earlier than what we proposed to our patients. In patients who experienced infectious complication under IFX, no further infection was observed after IFX withdrawal. Infectious complications have been reported in patients with sarcoidosis treated by TNF-α antagonists (20. 37), especially with intracellular bacteria (5. 37). These infections are usually severe but not fatal as was the case in our series. In the prospective studies reported by Baughman (30), serious adverse reactions were observed in 11% of cases. Maneiro *et al*. (17), reported adverse effects in 134/258 (51.9%) patients. The side effects were serious in 54 patients (21%) and included 76 infections, 6 malignancies, 2 disease progressions and 2 deaths (17). In these studies, no data are provided regarding either immunosuppressive therapy or treatment duration. We did not observe any malignancies and death due to side effects. Aside the side effect, one important issue for responders is the risk of relapse during treatment and/or after IFX withdrawal. Relapse during treatment impose escalation in IFX dosing and/or reduction of the interval between infusions. Out of our 3 relapse patients, reducing intercure interval was always necessary. Panselinas *et al*. (38) compared in a small retrospective study, the severity of involvement of the index organ from time of IFX discontinuation to the end of the following period in 14 patients. At 12 months, improvement was observed in 64% of cases and within 3 months of discontinuing IFX therapy 86% of patients relapse (38). Such relapses (38.39) impose a regular patient follow-up. Judson *et al*. (20) also reported relapse of sarcoidosis after IFX withdrawal and escalation in IFX dosing was required for the majority of patients with an average intercure interval of every 5.5 weeks. The mechanism of intercure relapse and progressive resistance seems likely due to immunisation and the occurrence of auto antibodies against IFX (in one case in our series). The combination with other IST could improve the therapeutic response while limiting the anti-IFX antibodies occurrence (40).

Despite several limitations of our series (small number of patients, retrospective data, single centre, non-randomised series), our results demonstrate that IFX is an effective therapeutic option in severe and refractory sarcoidosis. Infectious complications were frequent especially in patients in whom the duration of steroids and IST use prior to IFX was superior to 18 months. Relapses are frequent and frequently require escalation in IFX dosing and/or reduction of the interval between infusions.

References

1. BAUGHMAN RP, LOWER EE: Infliximab for refractory sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2001; 18: 70-4.
2. DOTY JD, MAZUR JE, JUDSON MA: Treatment of sarcoidosis with infliximab. *Chest* 2005; 127: 1064-71.
3. ROSSMAN MD, NEWMAN LS, BAUGHMAN RP *et al*.: A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2006; 23: 201-8.
4. HOSTETTLER KE, STUDLER U, TAMM M, BRUTSCHE MH: Long-term treatment with infliximab in patients with sarcoidosis. *Respiration* 2012; 83: 218-24.
5. RUSSELL E, LUK F, MANOCHA S, HO T, O'CONNOR C, HUSSAIN H: Long term follow-up of infliximab efficacy in pulmonary and extra-pulmonary sarcoidosis refractory to conventional therapy. *Semin Arthritis Rheum* 2013; 43: 119-24.
6. ROBERTS SD, WILKES DS, BURGETT RA, KNOX KS: Refractory sarcoidosis responding to infliximab. *Chest* 2003; 124: 2028-31.
7. JUDSON MA, BAUGHMAN RP, COSTABEL U, MACK M, BARNATHAN ES: The potential additional benefit of infliximab in patients with chronic pulmonary sarcoidosis already receiving corticosteroids: a retrospective analysis from a randomized clinical trial. *Respir Med* 2014; 108: 189-94.
8. RIANCHO-ZARRABEITIA L, DELGADO-ALVARADO M, RIANCHO J *et al*.: Anti-TNF-α therapy in the management of severe neurosarcoidosis: a reprot of five cases from a single centre and literature review. *Clin Exp Rheumatol* 2014; 32: 275-84.

9. DRENT M, CREMERS JP, JANSEN TL, BAUGHMAN RP: Practical eminence and experience -based recommandations for use of TNF-α inhibitors in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31: 91-107.
10. MILMAN N, GRAUDAL N, LOFT A, MORTENSEN J, LARSEN J, BASLUND B: Effect of the TNF-alpha inhibitor adalimumab in patients with recalcitrant sarcoidosis: a prospective observational study using FDG-PET. *Clin Respir J* 2012; 6: 238-47.
11. PARISER RJ, PAUL J, HIRANO S, TOROSKY C, SMITH M: A double-blind, randomized, placebo-controlled trial of adalimumab in the treatment of cutaneous sarcoidosis. *J Am Acad Dermatol* 2013; 68: 765-73.
12. ZIEGENHAGEN MW, BENNER UK, ZISSEL G, ZABEL P, SCHLAAK M, MULLER-QUERNHEIM J: Sarcoidosis: TNF-alpha release from alveolar macrophages and serum level of sIL-2R are prognostic markers. *Am J Respir Crit Care Med* 1997; 156: 1586-92.
13. PARK MK, FONTANA JR, BABAALI H *et al*.: Steroid-sparing effects of pentoxifylline in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2009; 26: 121-31.
14. FAZZI P, MANNI E, CRISTOFANI R *et al*.: Thalidomide for improving cutaneous and pulmonary sarcoidosis in patients resistant or with contraindications to corticosteroids. *Biomed Pharmacother* 2012; 66: 300-7.
15. PRITCHARD C, NADARAJAH K: Tumour necrosis factor alpha inhibitor treatment for sarcoidosis refractory to conventional treatments: a report of five patients. *Ann Rheum Dis* 2004; 63: 318-20.
16. YEE AM, POCHAPIN MB: Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. *Ann Intern Med* 2001; 135: 27-31.
17. MANEIRO JR, SALGADO E, GOMEZ-REINO JJ, CARMONA L: Efficacy and safety of TNF antagonists in sarcoidosis: data from the Spanish registry of biologics BIOBADASER and a systematic review. *Semin Arthritis Rheum* 2012; 42: 89-103.
18. CHAPELON C, ZIZA JM, PIETTE JC *et al*.: Neurosarcoidosis: signs, course and treatment in 35 confirmed cases. *Medicine* (Baltimore) 1990; 69: 261-76.
19. CHAPELON-ABRIC C: Cardiac sarcoidosis. *Curr Opin Pulm Med* 2013; 19: 493-502.
20. JUDSON MA, BAUGHMAN RP, COSTABEL U *et al*.: Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J* 2008; 31: 1189-96.
21. MALLBRIS L, LJUNGBERG A, HEDBLAD MA, LARSSON P, STAHLE-BACKDAHL M: Progressive cutaneous sarcoidosis responding to anti-tumor necrosis factor-alpha therapy. *J Am Acad Dermatol* 2003; 48: 290-3.
22. THIELEN AM, BARDE C, SAURAT JH, LAFFITTE E: Refractory chronic cutaneous sarcoidosis responsive to dose escalation of TNF-alpha antagonists. *Dermatology* 2009; 219: 59-62
23. STAGAKI E, MOUNTFORD WK, LACKLAND DT, JUDSON MA: The treatment of lupus pernio: results of 116 treatment courses in 54 patients. *Chest* 2009; 135: 468-76.
24. ROSEN T, DOHERTY C: Successful long-term management of refractory cutaneous and upper airway sarcoidosis with periodic infliximab infusion. *Dermatol Online J* 2007; 13: 14.
25. MORAVAN M, SEGAL BM: Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil. *Neurology* 2009; 72: 337-40.
26. MENON Y, CUCURULL E, REISIN E, ESPINOZA LR: Interferon-alpha-associated sarcoidosis responsive to infliximab therapy. *Am J Med Sci* 2004; 328: 173-5.
27. HUFFSTUTTER JG, HUFFSTUTTER JE: Hypercalcemia from sarcoidosis successfully treated with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2012; 29: 51-2.
28. KEIJSERS RG, VERZIJLBERGEN JF, VAN DIEPEN DM, VAN DEN BOSCH JM, GRUTTERS JC: 18F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25: 143-9.
29. MILMAN N, ANDERSEN CB, BASLUND B, LOFT A, IVERSEN M: Does tumour necrosis factor-alpha inhibitor infliximab induce histological resolution of pulmonary sarcoid granulomas? *Clin Respir J* 2007; 1: 106-13.
30. BAUGHMAN RP, SHIPLEY R, DESAI S *et al*.: Changes in chest roentgenogram of sarcoidosis patients during a clinical trial of infliximab therapy: comparison of different methods of evaluation. *Chest* 2009; 136: 526-35.
31. CROUSER ED, LOZANSKI G, FOX CC, HAUSWIRTH DW, RAVEENDRAN R, JULIAN MW: The $CD4^+$ lymphopenic sarcoidosis phenotype is highly responsive to anti-tumor necrosis factor-{alpha} therapy. *Chest* 2010; 137: 1432-5.
32. SWEISS NJ, BARNATHAN ES, LO K, JUDSON MA, BAUGHMAN R: C-reactive protein predicts response to infliximab in patients with chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2010; 27: 49-56.
33. JAMILLOUX Y, NEEL A, LECOUFFE-DESPRETS M *et al*.: Progressive multifocal leukoencephalopathy in patients with sarcoidosis. *Neurology* 2014; 82: 1307-13.
34. DAIEN CI, MONNIER A, CLAUDEPIERRE P *et al*.: Sarcoid-like granulomatosis in patients treated with tumor necrosis factor blockers: 10 cases. *Rheumatology* (Oxford) 2009; 48: 883-6.
35. MASSARA A, CAVAZZINI L, LA CORTE R, TROTTA F: Sarcoidosis appearing during anti-tumor necrosis factor alpha therapy: a new "class effect" paradoxical phenomenon. Two case reports and literature review. *Semin Arthritis Rheum* 2010; 39: 313-9.
36. VIGNE C, TEBIB JG, PACHECO Y, COURY F: Sarcoidosis: an underestimated and potentially severe side effect of anti-TNF-alpha therapy. *Joint Bone Spine* 2013; 80: 104-7.
37. JOUNIEAUX F, CHAPELON C, VALEYRE D *et al*.: [Infliximab treatment for chronic sarcoidosis--a case series]. *Rev Mal Respir* 2010; 27: 685-92.
38. PANSELINAS E, RODGERS JK, JUDSON MA: Clinical outcomes in sarcoidosis after cessation of infliximab treatment. *Respirology* 2009; 14: 522-8.
39. VORSELAARS AD, VERWOERD A, VAN MOORSEL CH, KEIJSERS RG, RIJKERS GT, GRUTTERS JC: Prediction of relapse after discontinuation of infliximab therapy in severe sarcoidosis. *Eur Respi J* 2014; 43: 602-9.
40. BAUGHMAN RP, LOWER EE, DRENT M: Inhibitors of tumor necrosis factor (TNF) in sarcoidosis: who, what, and how to use them. *Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25: 76-89.